



# Chronic Toxicity Study of Ethanol Extract from *Voacanga foetida* (Blume) Rolfe Leaves on Liver Biochemical and Histopathological Parameters in Male White Rats (*Rattus norvegicus*)

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**ABSTRACT:** This study aimed to evaluate the chronic toxicity of the ethanol extract of *Voacanga foetida* (Blume) Rolfe leaves on liver biochemical and histopathological parameters in male white rats (*Rattus norvegicus*). The animals were orally administered the extract daily for six months and divided into four groups: a control group and three treatment groups receiving doses of 70, 140, and 210 mg/kg body weight (BW), respectively. Biochemical analyses included serum levels of albumin, total bilirubin, SGOT, SGPT, and triglycerides. Liver histopathological changes were observed both macroscopically and microscopically. The results showed that ethanol extract administration at all tested doses did not cause significant changes ( $p > 0.05$ ) in albumin, total bilirubin, SGOT, or triglyceride levels compared to the control. However, SGPT levels were significantly elevated ( $p < 0.05$ ) in the 140 and 210 mg/kg BW groups. Macroscopic examination revealed no alterations in liver color or texture across all groups. Microscopic observations indicated no structural damage to the central vein in the liver ( $p > 0.05$ ). In conclusion, subchronic oral administration of ethanol extract from *V. foetida* leaves up to 210 mg/kg BW for six months did not produce significant toxic effects on liver function or morphology in male rats.

**Keywords:** *Voacanga foetida*; ethanol extract; chronic toxicity; SGPT; liver histopathology.

## Introduction

The *Voacanga foetida* (Blume) Rolfe from the Apocynaceae family, is used for its antifungal, antibacterial, anticancer, analgetic, and skin disease properties [1-7]. Researchers have previously conducted in vivo cytotoxicity tests using the micronucleus assay method. They reported that the ethanol extract derived from *V. foetida* leaves, administered at doses of 100, 200, and 300 mg/kg BW, exhibited anti-carcinogenic activity [8]. The researcher also conducted an acute toxicity test on the ethanol extract derived from *V. foetida* leaves. The results indicated that the ethanol extract of *V. foetida* leaves was categorized as practically non-toxic, with an LD<sub>50</sub> value > 15 g/kg BW [8].

The liver plays a role in metabolic and excretory functions in the body. This organ is involved in the metabolism of food substances, most drugs, and poisons. Toxicants can cause toxic effects on various liver cell organelles, resulting in types of liver damage, such as fatty liver, liver necrosis, cholestasis, cirrhosis, and so on. Several biochemical parameters related to the liver include

albumin levels, total bilirubin, as well as the activities of SGOT and SGPT, and triglyceride levels. Although plants of the species *V. foetida* are widely used in medicine, there have been no reports regarding their effect on the biochemical parameters of the liver after six months of use. In particular, long-term subchronic exposure to *V. foetida* leaf extract has not yet been systematically studied for its potential hepatotoxicity, leaving a gap in understanding regarding its safety profile. The lack of preclinical data on liver function markers after extended administration raises critical questions about the potential risks of chronic use.

Based on these considerations, it is necessary to examine the potential systemic effects that may arise from the administration of the ethanol extract of *V. foetida* leaves for six months on the liver's biochemical parameters in male white rats (*Rattus norvegicus*). This examination involves measuring levels of albumin and total bilirubin, as well as the activities of SGOT and SGPT,

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along with the measurement of triglyceride levels. The results of this study will provide crucial information to fill the current knowledge gap and help assess the safety of further clinical trials and the future development of phytopharmaceuticals derived from *V. foetida*. Therefore, this study aims to answer the question: Does long-term administration of ethanol extract of *V. foetida* leaves affect key liver biochemical parameters in male white rats.

## Methods

### Materials

The research materials included *V. foetida* leaves, 96% ethanol, NaCMC, distilled water, albumin reagent solution (Diasys®), total bilirubin reagent solution (Diasys®), SGOT reagent solution (Diasys®), SGPT reagent solution (Diasys®), and triglyceride reagent solution (Diasys®). The equipment utilized in this research included a rotary evaporator, analytical balance, animal scales, oral needle, filter paper, micropipette, test tube, centrifuge, and spectrophotometer (Microlab 300).

### Sample

The leaves of the *V. foetida* from the Anai Valley area, Padang Panjang, West Sumatra. Identification was at the Botany Laboratory, Department of Biology, Faculty of Mathematics and Natural Sciences, Andalas University.

### Extraction

The extraction was performed using the maceration method. The maceration process was carried out for five days, with three replications and occasional stirring. After maceration, the resulting mixture was filtered through cotton and transferred into a closed vessel. Subsequently, it was concentrated using a rotary evaporator.

### Preparation of Experimental Animals

The experimental animals were male *Wistar* Strain *Rattus norvegicus* obtained from Andalas University, weighing between 130–150 g and approximately two months old. They underwent an acclimatization period, and their body weights were maintained within  $\pm 10\%$  of the initial weight throughout the experiment. The rats exhibited normal behavior based on visual observation. The animals were housed under controlled conditions, including normal lighting, a temperature of 22°C, and humidity levels maintained between 30% and 70%. They were kept in a clean environment, with food and water provided *ad libitum* throughout the study.

### Dosage Preparation

The doses used in this study were 70, 140, and 210 mg/kg of BW, administered orally. The volume of the solution given to the animals was calculated based on a formula:

$$\text{VAO (mL)} = \frac{(\text{Body (-Weight (kg))} \times \text{Dosage (mg//kg Body-Weight)})}{\text{Concentration(mg//mL)}}$$

VAO: Drug Administration Volumes

### Treatment of Experimental Animals

The experimental animals were divided into four groups, each consisting of five rats: three treatment groups and one negative control group. The treatment groups received an oral suspension of ethanol extract from *V. foetida* leaves at a predetermined dose via a feeding tube, while the control group was given a 1% Na CMC suspension equivalent to 1% of each rat's body weight. The administration was carried out orally once daily for 180 days.

On the 181<sup>st</sup> day, blood samples were collected using the ophthalmic method. Before blood collection, topical anaesthesia was applied to the eye. The rat was held securely by gripping the shoulder area with the thumb and forefinger while pulling the skin around the eye firmly. Blood was drawn using a capillary tube inserted at a 30-degree angle into the medial canthus of the eye until it reached the venous plexus/sinus. Once 2 mL of blood was collected, the capillary tube was gently removed, and a sterile cotton swab was used to stop any bleeding by applying light pressure. The collected blood was transferred to an Eppendorf tube and centrifuged at 4000 rpm for 10 minutes at room temperature. The serum was then separated and used to measure albumin, total bilirubin, SGOT, SGPT, and triglyceride levels.

### Measurement of Albumin Levels

The albumin levels were measured using the Bromocresol Green Photometrics Test method at a wavelength of 546 nm. The principle of the reaction is that in the presence of green bromocresol in an acidic medium, the color changes from yellow-green to green-blue.

### Measurement of Total-bilirubin Levels

Total bilirubin levels were measured using the Jendrosik Grof method. In this reaction, total bilirubin reacts with diazotized sulphanilic acid (DSA) to form red azo compounds under acidic and neutral conditions. For

sample preparation, 100  $\mu\text{L}$  of Reagent 1 was pipetted into a test tube, followed by the addition of 25  $\mu\text{L}$  of Reagent 2, 500  $\mu\text{L}$  of Reagent 3, and 100  $\mu\text{L}$  of the sample. The mixture was homogenized and incubated at room temperature for 10 minutes. Subsequently, 100  $\mu\text{L}$  of Reagent 4 was added, and the incubation continued for another 5 minutes at room temperature. The absorbance was then measured using a spectrophotometer (MicroLab 300) at 578 nm.

### SGOT and SGPT Activity Measurement

The UV Test method based on the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) was used.

### Manufacturing of mono-reagents

The mono-reagent was prepared by combining reagent 1 and reagent 2 in a ratio of 4:1 for the first step, followed by mixing reagent 1 and reagent 2 in a ratio of 1:1 until homogeneous.

### Sample Preparation

To measure SGOT and SGPT levels, 60  $\mu\text{L}$  of serum was pipetted into a test tube, followed by the addition of 600  $\mu\text{L}$  of SGOT/SGPT mono reagent. The mixture was homogenized and incubated at room temperature for 1 minute before absorbance was measured using a spectrophotometer (Micro-Lab 300) at 340 nm. Absorbance readings were repeated at the 1st and 2nd minutes.

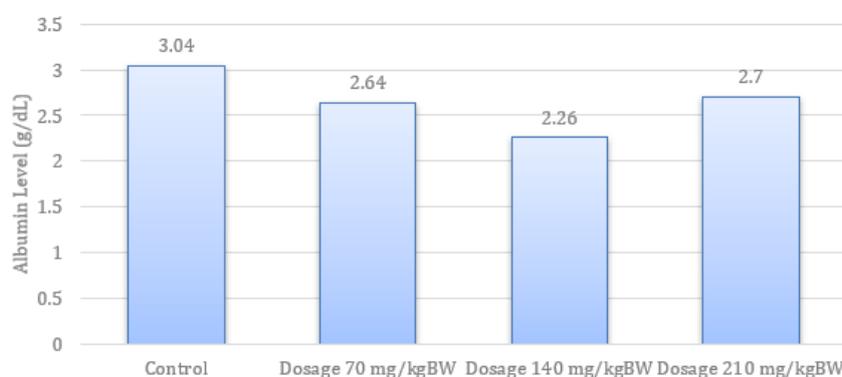
Triglyceride levels were determined using the Glycerol-3-Phosphate Oxidase (GPO) method. In this

reaction, triglycerides were hydrolyzed to release glycerol, which then reacted with ATP in the presence of glycerol kinase to form glycerol 3-phosphate and ADP. Glycerol 3-phosphate was subsequently oxidized by glycerol phosphate oxidase into dihydroxyacetone phosphate and hydrogen peroxide. The resulting hydrogen peroxide reacted with aminophenazone and chlorophenols to produce a pink quinone, whose intensity was proportional to the triglyceride concentration in the sample.

### Preparation of Liver Histology

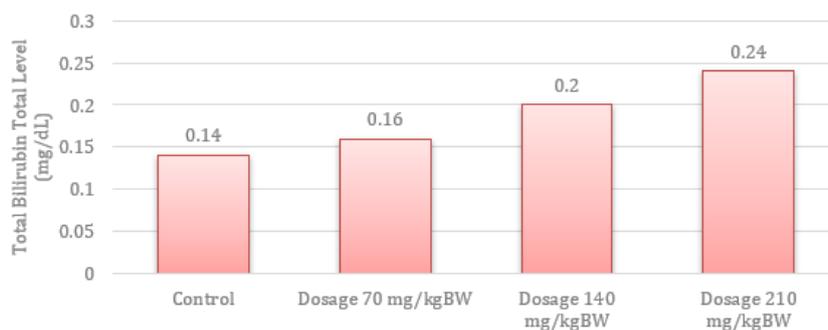
Liver tissue for histological examination was collected from animals euthanized by cervical dislocation following anesthesia with ether. The histological process began with fixation in a 10% formalin solution for 24 hours. Dehydration was performed using alcohol solutions of 70%, 80%, and 90% for 1 hour each, followed by absolute alcohol in three successive steps, also for 1 hour each. The tissue was then cleared using three xylene solutions for 15 minutes per step.

Following clearing, the tissue was impregnated and embedded in paraffin. It was first placed in a container with a 1:1 mixture of xylene and pure paraffin for 1 hour. After 30 minutes, the sample was transferred to a second container, then to a third containing liquid paraffin, for 1 hour each. The tissue was embedded in paraffin blocks, positioned on block plates, filled with liquid paraffin, covered with a cassette, and cooled on a cold plate for 24 hours. Thin tissue sections (5-6 microns) were cut using a microtome and placed in a 40°C water bath before being mounted onto gelatin-coated glass slides. The slides were heated in a slide warmer for 24 hours to ensure firm



**Figure 1.** Albumin levels of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

The graph shows the serum albumin levels (g/dL) in male white rats after 6 months of oral administration of ethanol extract of *V. foetida* leaves at doses of 70, 140, and 210 mg/kg BW compared to control. No significant differences were observed between treatment groups and control.



**Figure 2.** Total bilirubin levels of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

This figure illustrates total bilirubin concentrations (mg/dL) in serum after chronic administration of *V. foetida* leaf extract. The bilirubin levels remained statistically unchanged across all groups ( $p > 0.05$ ), suggesting normal hepatic function and no impairment in bilirubin metabolism.

adhesion.

For staining, the sections were immersed in three xylene solutions for 5 minutes each to clarify the tissue. Rehydration was performed using alcohol solutions of decreasing concentrations (96%, 80%, and 70%) for 5 minutes each. The sections were then stained with Hematoxylin for 5 seconds and Eosin for 10 minutes. Dehydration was carried out by briefly dipping the sections in alcohol solutions of increasing concentrations (70%, 80%, and 96%) for 5 seconds each. To enhance tissue clarity, the sections were placed in three xylene solutions for 10 minutes each. Finally, the samples were mounted with Entellan and examined under a microscope.

Qualitative parameters were observed based on changes in the central vein, hepatocyte cells, sinusoids, nucleus, and endothelium. However, the quantitative parameters were only assessed for the central vein. The central vein, being the largest and having a distinct shape

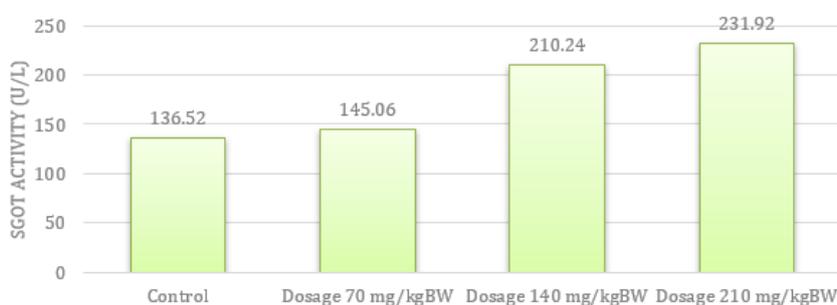
compared to the others, was counted with certainty.

### Data Analysis

The statistical analysis of the research data was carried out using the SPSS software. A one-way Analysis of Variance (ANOVA) was employed after performing a homogeneity test. When significant differences were detected, the analysis proceeded with the Tukey Post Hoc test to identify specific differences among the treatment groups.

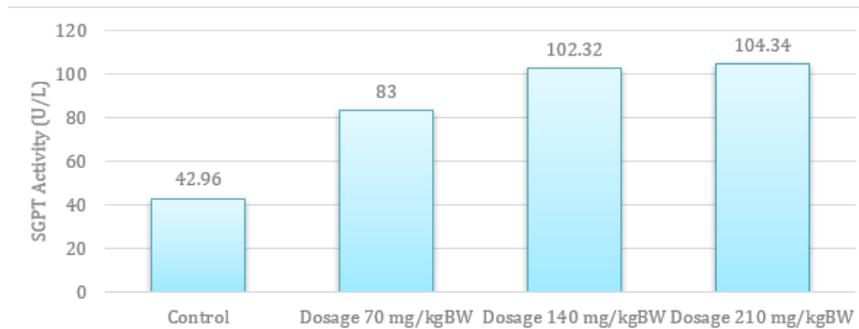
## Result and Discussion

The administration of *Voacanga foetida* ethanol extract at various doses did not significantly affect serum albumin levels. The mean albumin concentration in the control group was 3.04 g/dL, while the treatment groups receiving doses of 70, 140, and 210 mg/kg BW showed levels of



**Figure 3.** SGOT activity of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

Serum glutamic-oxaloacetic transaminase (SGOT) activities (U/L) showed no significant elevation in treated groups compared to controls ( $p > 0.05$ ), indicating that ethanol extract administration did not induce hepatocellular damage detectable by SGOT activity.



**Figure 4.** Sgpt activity of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

Serum glutamic-pyruvic transaminase (SGPT) levels (U/L) increased significantly at doses of 140 and 210 mg/kg BW compared to control ( $p < 0.05$ ), suggesting mild hepatocellular stress or injury at higher doses of *V. foetida* leaf extract.

2.64, 2.26, and 2.70 g/dL, respectively. Although these values were slightly lower, statistical analysis using one-way ANOVA demonstrated no significant differences among the groups ( $p > 0.05$ ), indicating that the extract did not impair hepatic synthetic function. These minor changes are likely attributable to hemoconcentration due to mild dehydration rather than liver dysfunction.

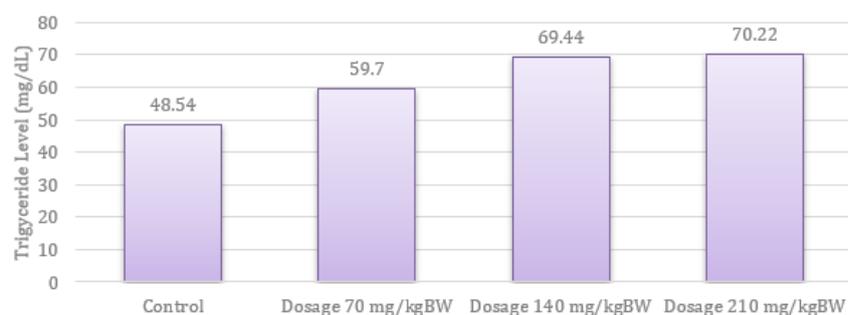
Similarly, total bilirubin levels increased in a dose-dependent manner, with the control group showing 0.14 mg/dL and the treated groups recording 0.16, 0.20, and 0.24 mg/dL, respectively. Despite this trend, the differences were not statistically significant ( $p > 0.05$ ), suggesting that the extract did not disturb bilirubin metabolism or biliary excretion pathways.

Assessment of liver enzyme activities revealed that SGOT levels rose from 136.52 U/L in the control group to 145.06, 210.24, and 231.92 U/L in the groups treated with 70, 140, and 210 mg/kg BW, respectively. In contrast, SGPT levels increased more markedly, from 42.96 U/L

in the control to 83.00, 102.32, and 104.34 U/L in the corresponding treatment groups. While the elevation in SGOT was not statistically significant ( $p > 0.05$ ), SGPT levels showed a significant increase at doses of 140 and 210 mg/kg BW ( $p < 0.05$ ), indicating mild hepatocellular injury. The greater elevation of SGPT compared to SGOT suggests early-stage cytoplasmic leakage, a typical marker of initial liver damage. However, the enzyme values remained within the range of subclinical or mild hepatotoxicity.

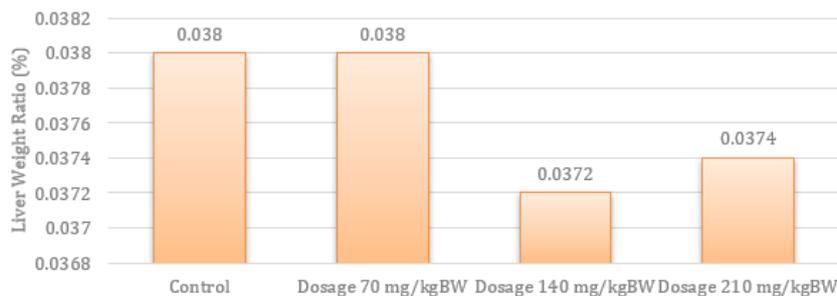
Serum triglyceride levels were also slightly higher in the treatment groups (69.44–70.22 mg/dL) compared to the control group (59.70 mg/dL), but the differences were not statistically significant ( $p > 0.05$ ). This finding implies that the extract did not significantly interfere with lipid metabolism or hepatic lipid regulation.

Regarding the liver-to-body weight ratio, values of 0.040 were recorded in the control group and 0.039, 0.036, and 0.036 in the treated groups. Although a mild decrease



**Figure 5.** Triglyceride levels of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

Triglyceride concentrations (mg/dL) remained stable and were not significantly different among the treatment groups and control ( $p > 0.05$ ), indicating that lipid metabolism was not adversely affected by the extract.



**Figure 6.** Liver weight ratio of male white rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

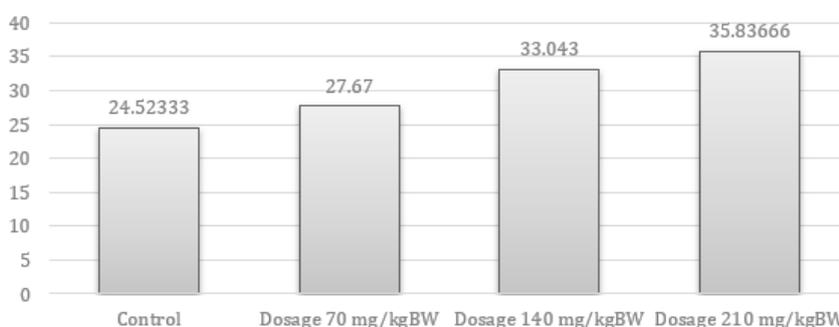
The relative liver weight (% of body weight) showed no significant differences across all groups ( $p > 0.05$ ), supporting the absence of gross hepatic hypertrophy or atrophy due to extract treatment.

was observed, no statistically significant differences were detected ( $p > 0.05$ ). These results indicate the absence of hepatomegaly or hepatic atrophy and support normal anatomical adaptation without signs of gross liver toxicity.

Finally, histopathological analysis revealed a gradual increase in central vein damage, progressing from 24.52% in the control group to 27.67%, 33.04%, and 35.83% in the extract-treated groups. Despite the observed trend, the differences were not statistically significant ( $p > 0.05$ ), suggesting that *V. foetida* extract did not induce substantial structural damage to hepatic central veins.

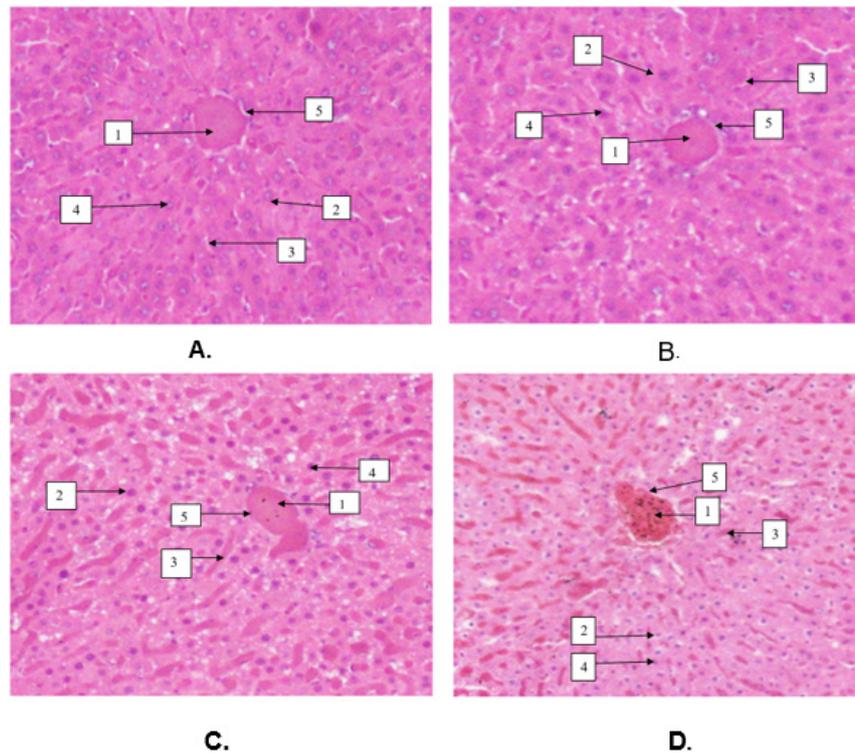
The present study aimed to evaluate the chronic toxicity of ethanol extract from *V. foetida* leaves on hepatic biochemical parameters and histopathology in male white rats over six months of oral administration. The parameters analyzed included serum albumin, total bilirubin, SGOT, SGPT, triglycerides, liver weight ratio, and microscopic liver tissue evaluation. Albumin levels remained consistent across all treatment groups and the

control, indicating that the synthetic function of the liver was not impaired by prolonged exposure to the extract. This aligns with previous research indicating that the albumin synthesis pathway is a reliable marker for liver functional integrity [9]. Similarly, total bilirubin levels showed no significant changes, suggesting that biliary excretion and hemoglobin catabolism processes were unaffected. Elevated bilirubin is often indicative of hepatobiliary dysfunction or hemolysis; thus, the stable levels observed suggest no cholestasis or hemolytic events [10]. Regarding transaminase activities, SGOT values remained unaltered, consistent with the absence of extensive hepatocyte damage. However, the significant elevation of SGPT (ALT) at 140 and 210 mg/kg BW doses indicates mild hepatocellular stress or membrane leakage. SGPT is more liver-specific than SGOT, and its increase suggests some degree of hepatic cellular perturbation at higher doses [11]. This finding implies that although the extract is generally safe, higher doses may warrant caution



**Figure 7.** Percentage of central vein damage to the liver of rats treated for 6 months with ethanol extract of *Voacanga foetida* leaves.

Histopathological examination revealed no significant difference in central vein damage (%) among control and treated groups ( $p > 0.05$ ), confirming no microscopic vascular injury in the liver after prolonged extract exposure.



**Figure 8.** Histopathology of the Liver in Experimental Animals (control (A), doses of 70 (B), 140 (C), and 210 mg/kg BW (D) from *V. foetida* extract) after 6 months treatment (Erlich Hematoxylin and Eosin staining). Description. 1. Central vein, 2. Hepatocyte, 3. Sinusoid, 4. Nucleus, 5. Endothelium.

due to potential subclinical liver injury. Triglyceride levels were not significantly affected by treatment, suggesting that lipid metabolism and storage functions of the liver remained intact. Alterations in triglycerides often reflect metabolic disturbances or hepatic steatosis, which were not observed here [12].

The liver weight ratio also showed no significant variation, which supports the absence of gross morphological changes such as hepatomegaly or atrophy that could occur due to toxic insult. Finally, histopathological examination of liver tissue focusing on central vein damage showed no significant differences among groups, corroborating the biochemical data indicating minimal to no liver structural damage. This microscopic evidence confirms that chronic administration of ethanol extract from *V. foetida* leaves up to 210 mg/kg BW does not induce overt hepatotoxicity. Ethanol extract of *V. foetida* leaves is relatively safe when administered chronically at doses up to 210 mg/kg BW, although the observed mild elevation in SGPT at higher doses suggests the need for further safety evaluation and dose optimization. These results support the ethnomedicinal use of *V. foetida* while underscoring the importance of monitoring liver enzymes during prolonged use. At 70 mg/kg BW, hepatocytes

and central veins appeared largely preserved, with mild sinusoidal dilation and fat vacuolation. At 140 and 210 mg/kg BW, more pronounced alterations occurred: sinusoidal congestion, central vein dilation, fatty degeneration, and hepatocyte necrosis (Figure 8). These changes suggest impaired hepatic outflow and parenchymal stress. Despite these microscopic lesions, biochemical parameters did not indicate significant functional hepatic impairment. Microscopic examination of liver tissue following six months of daily administration of *V. foetida* ethanol extract revealed dose-dependent histopathological changes (Figure 8). In the control group, hepatic architecture was well-preserved, characterized by intact central veins lined with continuous endothelial cells, organized sinusoids, and structurally normal hepatocytes. At the lowest dose of 70 mg/kg BW, liver morphology remained mostly intact, though minor fatty vacuolization indicated initial signs of steatosis. Increasing the dose to 140 mg/kg BW resulted in mild dilation of the central vein, endothelial cell damage, and sinusoidal congestion, along with moderate fatty degeneration. At the highest dose tested (210 mg/kg BW), more pronounced structural disruptions were observed, including marked steatosis, endothelial lining disruption of the central vein, congestion, and focal areas

of hepatocyte necrosis.

Crucially, the doses eliciting these hepatic changes (140–210 mg/kg BW) are substantially higher than the effective therapeutic doses reported in the literature. Anticancer activity of *V. foetida* alkaloids has been demonstrated at doses below 20 µg/kg BW [1,3,7,13-20], whereas analgesic, antipyretic and antiinflammation effects manifest around 250 mg/kg BW [2,21,22]. The present study confirmed that even doses at or above these therapeutic levels did not induce significant liver tissue damage, supported by stable serum biochemical markers and unchanged organ weight ratios. These findings affirm that the therapeutic application of *V. foetida* extract within pharmacologically relevant dosing regimens remains within a safe margin concerning hepatic integrity. This safety profile aligns with evidence from studies of other medicinal plants containing analogous alkaloids. For instance, aqueous extracts of *Bidens pilosa* and *Cymbopogon citratus* administered at various doses for 28 days did not result in substantial hepatic or renal toxicity, despite minor biochemical fluctuations [12,13]. Similarly, subchronic exposure to methanolic extract of *Euphorbia hirta*, also rich in alkaloids, showed no significant biochemical or histopathological liver alterations over 90 days in rats [14]. Notably, the current histological assessment involved prolonged exposure (181 days), which considerably exceeds typical clinical usage durations. Analgesic treatments generally last no more than 5 to 7 days, and anticancer therapies utilize significantly lower alkaloid doses. Therefore, the minimal hepatic changes observed after extended subchronic administration support the notion that *V. foetida* extract is well tolerated when used at therapeutic doses for shorter periods. Overall, this study provides preclinical evidence supporting the hepatic safety of *V. foetida* ethanol extract for potential analgesic and anticancer applications, provided that dosing adheres to established pharmacological guidelines. Continued monitoring of liver function in clinical settings is recommended to further ensure patient safety.

## Conclusion

This study demonstrated that prolonged daily administration of *V. foetida* ethanol extract for 181 days induced only mild, dose-dependent histopathological changes in liver tissue, without significant impairment of liver function. Importantly, the doses at which therapeutic effects such as analgesia (approximately 250 mg/kg BW) and anticancer activity (below 20 µg/kg BW) occur are substantially lower and administered for much shorter

durations in clinical practice.

Therefore, *V. foetida* extract is considered safe for use within these therapeutic dose ranges and treatment periods. The liver's tolerance to prolonged exposure further supports its favorable safety profile, justifying the continued investigation and potential application of *V. foetida* as a natural analgesic and anticancer agent. Nonetheless, further clinical studies are warranted to validate these findings in human subjects and to optimize dosing regimens for maximum efficacy and safety.

## Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

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